Consideration of Mode of Action Data is Critical for Formaldehyde Risk Assessment

Formaldehyde is a widely used high production chemical and is also a chemical produced as part of normal physiologic processes in all living cells. It represents one of the most extensively studied chemicals, with more than 30 years of research focused on understanding the potential for the development of cancer following inhalation of formaldehyde. The research that has been conducted falls into 3 general types of studies: epidemiological, animal, and mode of action (MOA). While the epidemiological and animal studies focus on the identification of health effects that may be associated with formaldehyde exposure, the MOA research focuses specifically on trying to understand how formaldehyde exposure could result in the development of a specific health effect. If hypothetical mechanisms are proposed, MOA research provides a way to determine whether or not these proposed mechanisms are biologically plausible.

Regulatory Assessments Lacking Integration of MOA

In reviewing the available research for formaldehyde, US regulatory programs (EPA IRIS, NTP Report on Carcinogens) have suggested an association between formaldehyde exposure and nasopharygeal cancer (NPC) or lymphohematopoietic cancers (LHP), including myeloid leukemia. In addition, the USEPA IRIS program has developed draft toxicity values to characterize the potential risk formaldehyde exposure may contribute to the development of these types of cancers. However, what is missing from the current draft values is the consideration of mode of action data in drawing conclusions. The current assumption is that any level of formaldehyde exposure results in some level of potential cancer risk, which is inconsistent with the available MOA research.

The conclusions reached by the US programs are largely based on consideration of epidemiological studies in isolation, with no integration of evidence from both animal and mode of action studies. The need for this integration of evidence was noted by the National Academy of Sciences in its review of the draft IRIS Assessment. Since the animal and mode of action research provide no supporting evidence for the biological plausibility of LHP and evidence of mechanisms of NPC that would occur following exposure to high enough concentrations of formaldehyde to overwhelm normal repair processes, sole reliance on epidemiological studies is inappropriate.

Evidence from MOA Research Results

Because the formation of formaldehyde in the body is part of normal physiologic processes, it is necessary to consider the normal background levels of formaldehyde in the body and whether or not exposures to formaldehyde in the air can overwhelm these normal levels, leading to the increase in the potential for health effects. The available animal and mode of action research supports the need to consider this baseline level and establish evidence of concentrations below which cancers, specifically NPC, are not observed.

Regulatory Assessments Integrating MOA

The results from the MOA research provide evidence of a mechanism for NPC that has been relied upon by multiple authoritative bodies, including the European Chemicals Agency (ECHA) and the World Health

Organization (WHO), in drawing conclusions regarding the potential for carcinogenicity following inhalation of formaldehyde. These agencies have integrated the available evidence for formaldehyde carcinogenicity and have drawn very different conclusions than IRIS or NTP. The results from mode of action studies provide evidence that health effects following inhalation exposure to formaldehyde are limited to the portal of entry and are associated with exposure to high concentrations of formaldehyde. In considering MOA data related to NPC and LHP, ECHA concluded:

> "Altogether, in absence of convincing evidence for a biologically plausible mechanism and considering the discrepancy of results in epidemiological studies, a causal relationship between formaldehyde exposure and induction of myeloid leukaemia cannot be concluded."
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> "Experimental results and mechanistic data therefore support the existence of a threshold type dose-response for induction of nasal tumours with regenerative cell proliferation being the predominant feature in the carcinogenic process. The genotoxicity of formaldehyde is also expected to play a role above this threshold."
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> "Overall, there is no convincing evidence of a carcinogenic effect at distant sites or via other routes of exposure than inhalation."

Therefore, consideration of MOA data are critical in not only establishing the biological plausibility of selected cancers, but also to incorporate consideration of the understanding of how inhalation of formaldehyde may impact normal physiological levels and processes. Integration of these data into the early steps of the risk assessment process attempting to identify health effects that may be associated with inhalation of formaldehyde has resulted in different conclusions across agencies. These differences are largely due to whether or not MOA data are considered. Consideration of MOA data becomes even more critical in conducting the quantitative steps of a risk assessment to ensure that recommendations for acceptable exposures to formaldehyde are not below those levels normally present in the body. It will also ensure those recommendations are consistent with our understanding of how health effects may occur following exposure to formaldehyde. Further, incorporation of MOA data into the risk assessment process follows the current state-of-the-science for regulatory processes, guidelines and regulations, which are shifting to a focus on evidence integration, specifically from the three "streams" of evidence, as well as consideration of study quality.

Methods to Incorporate MOA into the Risk Assessment Process

Tools currently exist that will allow for the incorporation of MOA data into the quantitative risk assessment for formaldehyde. A biologically-based dose-response (BBDR) model has been developed that relies upon decades of MOA research to provide a clear quantitative description of the delivery of formaldehyde to the nasal tissues and characterize the cellular mechanisms of formaldehyde carcinogenicity. This model has been used in previous EPA regulatory decisions regarding acceptable air concentrations for formaldehyde. Incorporation of this model, as well as other existing MOA data, are critical in conducting any risk assessment for formaldehyde. This will ensure regulatory decisions and recommendations for acceptable levels of exposure are determined based on the best available science and our current understanding of how exposure to formaldehyde may result in health effects.